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SCHISTOSOMIASIS: A MULTIPLICITY OF IMMUNOPATHOLOGY

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Human schistosomiasis involves three different species of blood flukes (*Schistosoma mansoni*, *S. japonicum*, and *S. haematobium*) which produce a series of disease states (swimmer's itch, Katayama fever, glomerulonephritis, and chronic organ inflammation and fibrosis) involving multiple immunologic mechanisms and responses [1]. These reactions involve three different multicellular stages of the parasite within the mammalian host—the schistosomula (immature schistosomes), adult schistosomes, and eggs. On contact with the skin the infective larva (cercaria) secretes enzymes and other antigenic material. During the penetration process the cercaria loses its tail, and on entering the skin becomes a schistosomulum (130 × 30 μ) changing morphologically from an organism with a tri-laminate to one with a hepta-laminate tegument [2], physiologically from a freshwater to a salt-water animal [3], and biochemically from oxidative metabolism to glycolysis [4]. During the penetration process many of these organisms die within the skin, the number being dependent on the susceptibility of the host to infection [5]. For a period of 2 to 4 days the schistosomula migrate through the dermis before passing in the circulatory system to the lungs, where they reach their peak concentration at 5 to 7 days [6]. During their tenure in the lungs they do not feed on red blood cells and growth does not occur. After 8 days the schistosomula begin to appear in the portal venules of the liver where they start to ingest erythrocytes and grow actively (6). By 26 days the young adult male (10 × 2 mm) and female (15 × 1 mm) worms commence mating and migrate to the mesenteric or vesical venous plexuses where eggs (160 × 60 μ) are laid.

The adult schistosomes do not replicate within the mammalian host, and their average life span appears to be between 5 and 10 years. During this period they produce 300 to 3,000 eggs per day in the mesenteric (*S. mansoni* and *S. japonicum*) or vesical (*S. haematobium*) venules. The eggs secrete enzymes through ultramicroscopic pores which facilitate their passage through the tissues into the lumens of the excretory organs. The majority of the eggs, however, never leave the body but are trapped within the host tissues where they live for approximately 3 weeks, die, and are slowly resorbed.

As described above, the host–parasite relation in schistosomiasis is complex, involving three different stages of the parasite within the host, each producing secretions, excretions, and breakdown products. Immunoelectrophoretic analysis using as antigens crude extracts of cercariae and eggs and secretions and excretions of adult worms maintained in vitro, and antisera prepared by injecting these antigens mixed with complete Freund's adjuvant into rabbits, revealed 12 to 13 bands in the cercarial and egg systems and 8 bands in the adult worm system [7]. When these antigens were tested against antisera from infected rabbits and monkeys, 5 to 7 bands were seen in each instance. Many of these antigens were cross-reacting; heterologous absorptions showing that the cercarial and egg antigens had more in common with each other than with adult worm secretions and excretions [7]. In a later study using antisera prepared in hyperimmunized rabbits and crude egg and adult worm antigens it was shown, also by immunoelectrophoresis, that the egg antigen has at least 20 components, 13 of which are common to adult worms [8].

In the past several years a circulating antigen has been demonstrated in the serum of massively infected small animals [9] which appears to be a polysaccharide originating in the gut of adult *S. mansoni* worms [10]. Recently, using the technique of acidification followed by double counter-current immunoelectrophoresis in hypertonic gels, and using a partially purified adult worm antigen and an antiserum from a chimpanzee with early *S. mansoni* infection, as many as 5 precipitin lines have been detected in the sera of humans infected with *S. mansoni* [11].

The enzymes which the cercariae release when they penetrate the skin do not seem to cause any significant pathology, either related to their enzymatic activity or immunogenicity, and they appear to play little if any role in the induction of immunity (A. Powell, personal communication). Penetrating cercariae, however, have been associated with the development of swimmer's itch, a papular pruritic rash. This reaction, also called schistosome dermatitis, occurs most often and is most severe when nonhuman, particularly avian, schistosomes penetrate the skin. Most, if not all, of these organisms die within the dermis. There is little evidence that *S. japonicum* cercariae produce

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swimmer's itch. This syndrome has been demonstrated in Egyptian subjects with known schistosome infections on exposure to large numbers of cercariae of *S. mansoni* and *S. haematobium* [12].

Swimmer's itch is a sensitization phenomenon, as the typical papules develop only in previously exposed individuals [13,14]. Relative specificity has also been demonstrated in humans exposed to avian and mammalian schistosomes [14]. The typical papules are delayed in onset and skin biopsies have revealed edema and massive round cell infiltration of the dermis and epidermis (13). Studies in experimental animals have demonstrated the relative lack of inflammation on primary exposure to cercariae and a recent report has described the passive transfer of the reaction (15). Sera from infected mice have been used to passively immunize normal mice, which then responded with early (5-hr) polymorphonuclear infiltrates against cercariae. Lymphoid cells from infected mice passively immunized normal mice which then developed late (30-hr) mononuclear infiltrates against cercariae or a cercarial extract. It was concluded that mice developed both humoral and cell-mediated immune responses against the cercarial stage of *S. mansoni* [15]. Repeated exposure of a monkey to massive numbers of x-irradiated cercariae resulted, on challenge with normal cercariae, in a marked eosinophilic response which appeared to be associated with destruction of schistosomula in the skin [16].

Studies of the passive transfer of immunity in mice with a new technique involving the isolation and counting of schistosomula in the lungs suggest that these organisms are killed either in the skin, during their migration to the lungs, or in the very earliest lung phase [17]. Recently it has been reported that anti-eosinophil serum given to partially immune mice from days −1 to +5 after infection abrogates the immunity as seen on day 6 [18]. Studies now in progress by this same group have revealed no effect when treatment with anti-eosinophil serum was begun at 3 days, suggesting that the schistosomula are destroyed largely in the skin. These findings are consistent with the concept of concomitant immunity in schistosomiasis advanced by Smithers' group and recently clarified further by McLaren et al [19]. During the first few days after cercarial penetration schistosomula, removed from the tissues and cultured in immune rhesus serum and complement, bind antibody to their surface membranes, suffer damage to the tegument, and are killed. When removed after 4 days within mice the surface of the schistosomula contains mouse erythrocyte antigens, it no longer binds monkey antibodies in vitro and the schistosomula are not killed [19].

The organisms, which survive skin penetration and the relatively inefficient host immunologic defense mechanisms, continue their migration from the lungs to the liver where they mate and pass down into the mesenteric and vesical plexuses. There is little evidence that any significant immune responses or pathology are occurring at this point. Soon after the worms commence egg laying, a condition known as Katayama fever may develop which is characterized by fever, eosinophilia, splenomegaly, lymphadenopathy, urticaria, and often diarrhea or dysentery. It occurs most frequently in schistosomiasis japonica, is usually seen in heavy primary infections, and has rarely if ever been reported in chronically infected individuals [1].

While the mechanism of Katayama fever remains unknown, it is possible that it may be a form of immune complex disease or serum sickness. In the earliest stages of schistosome infections, antibody formation is stimulated by penetrating cercariae and migrating schistosomula, but the levels of antibody are relatively low. Then oviposition begins in which many thousands of eggs may be produced daily in the heavily infected host. As many of the egg antigens cross-react with the worm antigens [7,8] antibody levels rise rapidly to meet this massive antigenic stimulus [20]. It is possible, therefore, that the condition of antigen excess conducive to the formation of soluble antigen–antibody complexes occurs at this point. The complexes may result not only in the occurrence of acute serum sickness, but also in the

TABLE. *Immunologic manifestations of the different stages of the life cycle of the schistosomes within the mammalian host*

	Antigens	Mechanisms
Swimmer's itch	Cercariae	Immediate and delayed hypersensitivity
Immunity	Schistosomula, schistosomes	Antibody-dependent cell-mediated killing
Katayama fever	Schistosomula, schistosomes, eggs	Antigen–antibody complexes
Glomerulonephritis (?)	Schistosomula, schistosomes, eggs	Antigen–antibody complexes
Chronic fibro-obstructive disease Hepatosplenomegaly Ureteral blockade Cor pulmonale	Eggs	Delayed hypersensitivity

development of glomerulonephritis which has been reported in patients with chronic schistosomiasis.

The latter was first suggested by Andrade and Queiroz [21] who observed an unusually high prevalence of renal lesions at autopsy of patients with schistosomiasis mansoni. Silva et al [22] found IgG and IgM complexes in kidney biopsy specimens of patients with *S. mansoni* infections with or without nephrosis. Nephritis of a variety of types has now been reported in many experimental animals including cebus monkeys with *S. mansoni* infections [23], chimpanzees with *S. japonicum* infections [24], rabbits [25], and mice [26]. These investigations are of importance, but await a closer association with clinical findings and the definitive demonstration of specific schistosome antigens or antischistosome antibodies in the kidneys. Further evidence for the possibility of complex-mediated disease has been provided by the recent report of circulating schistosome immune complexes in the serum of infected humans [11].

As described above, the mature worms produce large numbers of eggs, most of which remain in the body. Since the habitat of *S. mansoni* and *S. japonicum* is the blood vessels of the gut, that organ is involved primarily and the liver secondarily because of egg embolism. *S. haematobium* involves the urinary tract primarily and the lungs and liver secondarily. The egg surface evokes little or no inflammatory activity: on first exposure to eggs no cellular infiltrate is seen for approximately 2 to 3 days [27], and it has been shown that the eggs prolong the clotting time of Hageman factor-deficient plasma, suggesting anticoagulant and anti-inflammatory activity [28]. Granuloma formation appears to be related to the secretion of enzymes and other proteins and carbohydrates through ultramicroscopic pores in the egg shell. That these substances are antigenic has been demonstrated by the circumoval precipitin test using serum from infected subjects [29], by the use of fluorescent antibody [30], by output of sensitizing material by intact eggs in tissue culture, and by the sensitization achieved by eggs placed intraperitoneally in Millipore filters [31]. Further evidence for the role of secretions has been reported by Hang et al [27] who demonstrated that neither eggs in the early unembryonated stage nor embryonated eggs depleted of their antigens by prolonged tissue culture elicited granuloma formation on injection into mice.

Injection of intact living eggs or soluble egg antigens into animals results in sensitization, so that on secondary injection of eggs into the tissues there is an accelerated augmented inflammatory response. The reaction is specific as has been demonstrated by cross-sensitization studies with Ascaris eggs [32] (Fig. 1). Recent quantitative studies of the cell composition of the lesions have revealed that eosinophils, small mononuclear and large mononuclear cells each make up approximately 1/3 of the cells in the lesions. There are relatively few neutrophils and plasma cells are very

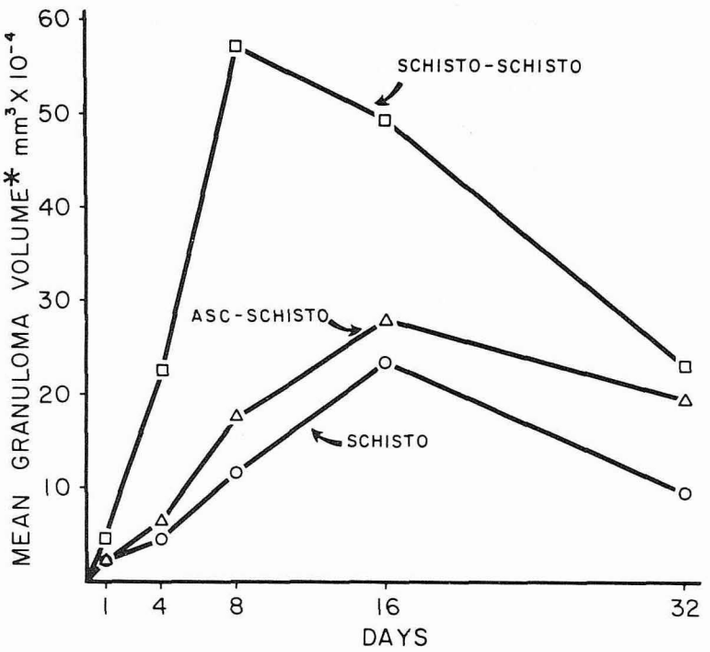

FIG. 1. Mean granuloma volumes around *Schistosoma mansoni* eggs 1 to 32 days after their intravenous injection into the pulmonary vasculature of unsensitized mice (*schisto*) and those immunized by a prior intraperitoneal injection of Ascaris (*asc-schisto*) or schistosome eggs (*schisto-schisto*). (*Calculated from mean granuloma diameter.)

rare [33]. Passive transfer of the anamnestic granulomatous response has been achieved with lymph node and spleen cells but not with serum [32] (Fig. 2). Fully developed granulomas have been observed in guinea pigs in the absence of any detectable IgG_1 or IgG_2 antibodies [34]. In both guinea pigs and mice the onset of an inflammatory reaction around the eggs occurs simultaneously with the appearance of delayed skin reactivity to soluble egg antigens [27,34]. The development of in vitro correlates of delayed hypersensitivity such as lymphocyte transformation and particularly macrophage migration inhibitory factor also occurs coincidentally with granuloma formation [34]. Measures which inhibit antibody formation such as x-irradiation [35] and Friend virus leukemia [36] have no effect on the granulomas, while those which tend to suppress delayed hypersensitivity such as thymectomy [37,38] and antilymphocyte serum [39] (Fig. 3) markedly inhibit granuloma formation. Recent studies with a drug, niridazole, which strongly suppresses delayed hypersensitivity [40], but has little or no effect on antibody formation [41], support the above findings. Finally, while bursectomized chickens showed no diminution in granulomatous response to schistosome eggs, those that were thymectomized neonatally had significantly smaller granulomas [42]. Intact granulomas have been isolated and maintained in vitro, and with or without subsequent exposure to antigen have been found to release two different lymphokines, migration inhibitory factor [43] and eosinophil stimulation promoter (D. G. Colley, personal communication; R. P. Pelley et al, work in progress). Thus, on the basis of the above results it has been established that the *S. mansoni* granu-

loma is an immunologic reaction of the delayed hypersensitivity type.

Strangely enough, the *S. japonicum* egg granuloma, which has always mystified investigators by the difference in its cellular composition from the *S. mansoni* lesion, appears to have a different etiology [44]. The inflammatory reactions occur around egg aggregates rather than single eggs. In the initial stages of infection eosinophilic abscesses appear, and large numbers of plasma cells are seen early in the course of the reaction. Soluble *S. japonicum* egg antigens induce marked immediate skin reactions and no delayed reactions, the responses being the reciprocal of those seen with *S. mansoni* egg antigens. Our working hypothesis at present is that the initial focal *S. japonicum* lesions may be the result of antigen–antibody complex reactions instead of delayed hypersensitivity.

The granulomatous inflammation around the schistosome eggs leads to tissue injury which is the result of replacement of normal tissue by the inflammatory infiltrate and may be fostered by the release of lysosomal enzymes by phagocytic cells [45]. When the eggs cease emitting their antigenic secretions and products of autolysis, a healing process ensues which is followed by scarring. The large avascular granulomas and the residual fibrous tissue both cause obstruction to portal blood flow in the liver [46], pulmonary blood flow in the lungs, and urine flow in the ureters.

Fortunately, a regulatory response appears to develop in which granuloma formation around new living eggs in the tissues gradually diminishes [47]. Recent studies from both our laboratory [48] and that of Colley [49] have revealed that this modulation occurs simultaneously with an increase in the level of antibody to soluble egg antigens and the development of unresponsiveness of lymphoid cells to these antigens. In addition, a generalized depression of lymphocyte transformation occurs both to specific antigen [49] and, nonspecifically, to mitogens [50]. Studies are in progress in our laboratory on the role of suppressor T-cells in the development of this phenomenon. The occurrence of this modulation of granulomatous hypersensitivity is probably an important factor in protecting the host against its immunopathologic responses to the schistosome eggs. Artificial stimulation of the modulating factors might lead to the development of a vaccine to prevent inflammation, scarring, and overt disease. In this regard, two antigens have now been isolated from *S. mansoni* in pure form by affinity chromatography, ion exchange chromatography, and gel filtration (R. P. Pelley et al, work in progress). These are glycoproteins of respective molecular weights of approximately 137,000 and 465,000 daltons. The smaller antigen elicits little antibody production as demonstrated by radioimmunoassay at 8 weeks when granuloma formation is at its peak, but there is a considerable amount of antibody at 30 weeks when modulation is markedly evident (R. P. Pelley et al, work in progress). Furthermore, this antigen shows virtually no cross-reactivity with soluble *S. japonicum* egg antigen.

In conclusion, human schistosomiasis not only involves three different species of schistosomes with differing biologic and antigenic characters, but each species has three different stages in the mammalian body. Multiple antibodies are pro-

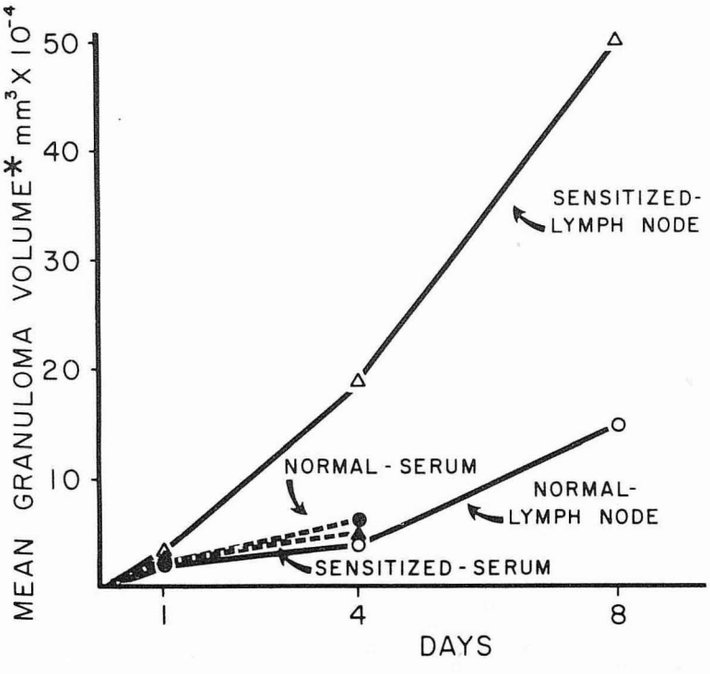

FIG. 2. Mean granuloma volumes around *Schistosoma mansoni* eggs 1 to 8 days after their intravenous injection into the pulmonary vasculature of mice which had received serum or lymph node cells from normal mice or those sensitized by infection with *S. mansoni*. (*Calculated from mean granuloma diameter.)

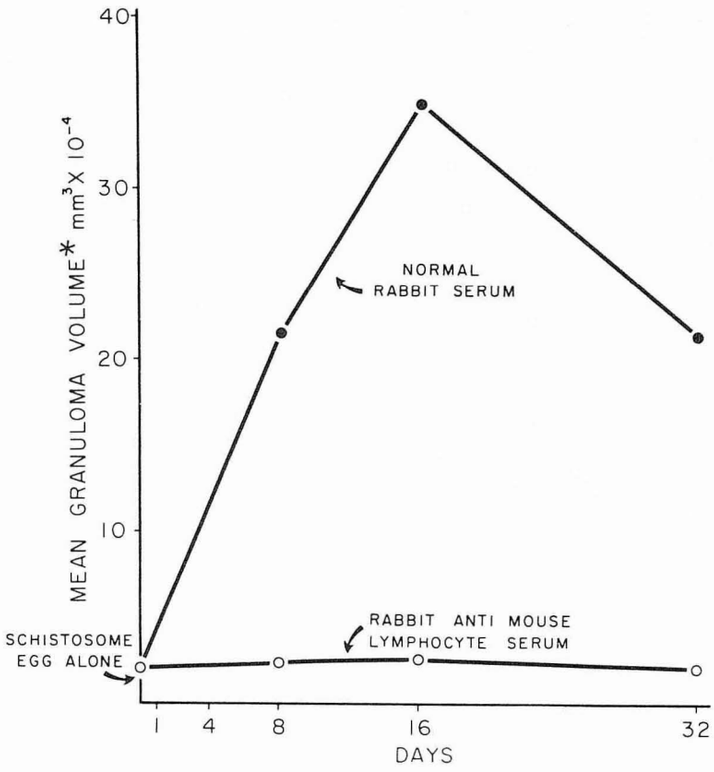

FIG. 3. Mean granuloma volumes around *Schistosoma manosoni* eggs 1 to 32 days after their intravenous injection into the pulmonary vasculature of mice treated by repeated injections of normal rabbit serum or rabbit antimouse lymphocyte serum. (*Calculated from mean granuloma diameter.)

duced in reaction to these organisms and a variety of cell-mediated responses have been reported. With respect to immunity (resistance to reinfection) a complement-requiring antibody which is lethal to schistosomula has been demonstrated in vitro [19] and an antibody-dependent, cell-mediated reaction against the worms in vivo has been described [18]. The clinical manifestations of infection appear to involve multiple antigens and different types of immunopathologic responses (Tab.). Thus, swimmer's itch is due to cercarial antigens which result in both 5-hr humoral antibody-mediated inflammation and delayed cell-mediated inflammation. Katayama fever may be an immune complex-mediated form of serum sickness due to cross-reacting antigens between the cercariae, worms, and eggs. The chronic glomerulonephritis which appears to occur in schistosomiasis may also be due to similar immune complexes. Hepatosplenic and urinary tract fibrotic disease is largely due to cell-mediated granuloma formation in response to antigens released by the eggs. There is considerable evidence that different antigens induce immunity and immunopathology in schistosomiasis, the former being due to worm and the latter to egg antigens. Massive injections of eggs did not induce immunity either in rhesus monkeys [51] or mice [52]. Conversely, neither unisexual infections, bisexual infections prior to egg laying, nor worm antigens sensitized animals to granuloma formation around schistosome eggs [53]. This places schistosomologists in a far better position than phthisologists or leprologists. because in contrast to the tubercle and lepra bacilli, immunity and hypersensitivity are directed against two different stages of the organism (neither of which multiply) and against different antigens. Thus, immunity can be fostered without enhancing immunopathology, and hypersensitivity can be suppressed without affecting resistance to infection. In the case of schistosomiasis, therefore, the multiplicity of immunologic responses may actually be beneficial by enabling the specific control of either the infection or the disease.

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DISCUSSION

Epstein: One other effect of chronic infection, not mentioned by you or Dr. Turk, is granulomatous hypersensitivity. In chronic cutaneous leishmaniasis the pathologic picture is an organized epithelioid cell granuloma, and we and Hsu have seen a similar action in chronic experimental schistosomiasis. It seems that when conventional immune responses are compromised in the face

of some chronic infections the mononuclear phagocyte system is activated to proliferate and produce a granuloma populated with epithelioid cells which can be secretory as we see in metal-induced granulomas. Thus, you must explain the zirconium granuloma which occurs in the apparent absence of measurable delayed hypersensitivity.

Warren: While I believe that morphology is the foundation of studies of pathologic lesions, I believe that it may be more important in the long run to classify granulomas by the mechanisms by which they are formed. A particular problem with epithelioid cells is that it is often difficult to get two pathologists to agree on the morphology of these cells. At a very recent international sarcoid meeting we presented a functional classification of granulomatous inflammation. Granulomas were divided into two groups—immunologic, in which anamnestic activity occurs, and non-immunologic granulomas, in which no anamnestic activity is seen. The *S. mansoni* egg granuloma is an example of the former, and the plastic bead granuloma is an example of the latter.

Turk: Epithelioid cell changes can readily be produced in macrophages in vitro in the presence of antigen and sensitized lymphocytes or by the action of lymphokine. Such cells show not only morphologic changes but also develop increased enzyme activity associated with the Krebs cycle and pentose shunt. I would challenge any evidence suggesting that epithelioid cells were other than the appearance of macrophages taking part in an immune reaction, whether cell-mediated or mediated by humoral antibody.

Austen: What are the IgE levels in schistosomiasis? What class of antibody is involved in antibody–eosinophil killing?

Warren: IgE levels have been shown by Colley to be elevated in mice with schistosomiasis. Interestingly enough, peak, heat-labile, PCA antibody levels occur in the acute stages of schistosomiasis; and as the immunoregulatory responses appear, the levels decline. This appears to be due to the fact that these antibodies are closely tied to T-helper-cell activity. IgE levels in humans with schistosomiasis have not been adequately studied. In most areas where schistosomiasis is endemic the patients have multiple helminth infections. When matching patients from two islands in the Caribbean were studied, one group with helminth infection with schistosomiasis and the other group without schistosomiasis, both groups had markedly elevated IgE levels but there were no significant differences between them. The antibody-dependent killing phenomenon has been described only recently, and, as far as I know, the nature of the antibody has not yet been determined.